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# Reproductive and hormonal factors and risk of brain tumors in adult females

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**Causes of brain tumors are largely unknown, and there is an urgent need to identify possible risk factors. Several observations point to a possible role of reproductive hormones, but few epidemiologic studies have examined whether reproductive factors, such as age at menarche and parity, are associated with brain tumor risk. We conducted a multi-center case-control study of newly diagnosed glioma ($n$ = 212) and meningioma ($n$ = 151) and frequency-matched controls ($n$ = 436) in women from hospitals in Phoenix, Arizona; Boston, Massachusetts; and Pittsburgh, Pennsylvania between 1994 and 1998. Research nurses interviewed patients regarding potential risk factors for brain tumors, including reproductive factors and hormone use. Unconditional logistic regression analyses were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Risk of glioma increased with older age at menarche [OR = 1.90 (95% CI = 1.09–3.32) for age at menarche ≥14 *vs.* <12 years]. Early age at first birth was associated with reduced risk of glioma [OR = 0.43 (95% CI = 0.23–0.83) for a first birth before age 20 *vs.* nulliparity], but there was little effect of number of births. Exogenous hormone use was also associated with a lower risk of glioma, but risks did not vary systematically according to duration of use or age at first use. Possibly owing to low statistical power, there were few noteworthy associations between meningioma and reproductive factors, other than a nonsignificant ($p$ = 0.09) trend of increasing risk with increasing age at menopause. The findings suggest that hormonal exposures early in life may be associated with risk of glioma, but the evidence is inconsistent and does not point clearly to a specific causal or protective hypothesis.**


**Key words:** brain tumors; reproductive factors; glioma; meningioma; parity; age at menarche; case-control study

The etiology of brain tumors is largely unknown. The only confirmed risk factors, high doses of ionizing radiation and certain rare genetic conditions, explain only a small fraction of the total cases.[1] A diverse list of potential risk factors for brain tumors includes a variety of occupational exposures, dietary factors and medical conditions, but, in most instances, the evidence is weak or inconsistent. Because of the poor prognosis for most types of adult brain tumor, new etiologic clues are urgently needed.

Several lines of evidence point to a possible role of reproductive hormones in brain tumor etiology. During childhood, the incidence of glioma in males and females is approximately equal, but males have higher rates beginning in early adolescence, suggesting possible protective effects of female hormones or, conversely, increased risks associated with exposure to androgens.[2] Among adults, the risk of glioma is approximately 50% higher in males. In the U.S., the age-adjusted incidence rate of glioma in males is 7.5/100,000, compared to 5.2 among females[3]; the higher rates in males are consistent over time and internationally.[4,5] In contrast, the incidence of meningioma is approximately 2-fold higher in females,[3] and the female predominance is greatest during the reproductive years[6,7] when hormonal differences between the sexes are most pronounced. Rapid growth of meningiomas during pregnancy has been reported[8,9] and elevated risks of meningioma have been found after a first primary malignancy of the breast,[10] although the basis of this association is unclear. Steroid hormone receptors are expressed in glioma and meningioma tissue,[11,12] with androgen receptors predominating in gliomas and progesterone receptors in meningiomas. Mifepristone (RU-486), a progesterone antagonist, is used therapeutically to slow the growth of unresectable meningiomas[13] and has been shown to slow the proliferation of meningioma tumor cells *in vitro*.[14] Finally, studies of transplanted glioblastoma cell lines in mice[15] and rats[16] have found significantly faster tumor growth rate and poorer survival in males. Plunkett[16] found no survival differences between male rats and ovariectomized female rats but reported that treatment of ovariectomized females with estrogen resulted in slower tumor growth and better survival, similar to that in females with intact ovaries. Several epidemiologic studies have reported reduced risks of glioma among parous women,[17–20] whereas others found no association.[21–23] Few other studies of reproductive factors and brain tumors have been described. Here, we report the associations between reproductive factors, exogenous hormone use and the occurrence of glioma and meningioma in females, based on data from a large, hospital-based case-control study conducted in the United States between 1994 and 1998.

## Material and methods

### *Study population*

Details of our study have been described previously.[24,25] Eligible cases were newly diagnosed (first microscopic confirmation within 8 weeks preceding or during index admission to participating hospital) with intracranial glioma or neuroepitheliomatous tumors ($n$ = 489; ICD-O-2 codes 9380-9473 and 9490-9506), meningioma ($n$ = 197; ICD-O-2 9530-9538), or acoustic neuroma ($n$ = 96; ICD-O-2 9560) at 1 of 3 participating hospitals (St. Joseph's Hospital in Phoenix, Arizona; Brigham and Women's Hospital in Boston, Massachusetts; and Western Pennsylvania Hospital in Pittsburgh, Pennsylvania). The current analysis was restricted to the 212 gliomas and 151 meningiomas that occurred in females. All tumors were histologically confirmed. The control series ($n$ = 436) consisted of female patients hospitalized with a variety of other conditions, including circulatory ($n$ = 99), digestive ($n$ = 60) or musculoskeletal ($n$ = 92) diseases, trauma ($n$ = 86) and miscellaneous other conditions ($n$ = 99). Controls were frequency-matched to the total case series by age (±10 years), ethnicity and distance of residence (0–5 miles, >5–15 miles, >15–30 miles, >30–50 miles, >50 miles) from the hospital. All subjects were ≥18 years old, spoke English or Spanish, and lived within 50 miles of the hospital (or within Arizona for the Phoenix center). Among eligible female subjects, the response rates were

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89% among patients with glioma, 94% among patients with meningioma and 89% among the control patients. Institutional review boards at participating hospitals and the National Cancer Institute approved the study protocol. Informed written consent was obtained from all participating subjects or their proxy respondents.

*Data collection*

Experienced research nurses in each hospital enrolled and interviewed study subjects, using a computer-assisted personal interview conducted at the patient's bedside. The hour-long interview consisted of questions on reproductive history and hormone use, sociodemographic characteristics, medical and occupational history, family history of cancer, cellular telephone use and other personal behaviors. Interviews conducted solely with proxies, usually the spouse, were carried out if the index subject had died or was too ill to participate. A total of 15.6% of glioma patients, 9.2% of meningioma patients and 1.6% of controls had proxy respondents for the section on reproductive history.

*Statistical analysis*

Separate analyses were conducted for the 212 glioma and 151 meningioma cases compared to the 436 controls. Odds ratios and 95% confidence intervals were used as measures of association and precision between reproductive factors and brain tumor risk. The reproductive factors examined included age at menarche and first live birth, gravidity, parity, lactation history, menopausal status (premenopausal *vs*. postmenopausal), type of menopause (natural *vs*. other), age at menopause, bilateral oophorectomy, use of oral contraceptives and use of hormone replacement therapy (HRT) among postmenopausal women. Women who reported a recent bilateral oophorectomy (within 1 year) were considered to have their ovaries intact for the purposes of the analysis. Similarly, those with initial exogenous hormone use within 1 year of the date of diagnosis (or date of interview for controls) were counted as unexposed to HRT. Unconditional logistic regression models were employed to control simultaneously for the matching factors and other covariates. Potential confounding factors that were considered included marital status (currently married *vs*. not), educational attainment (≤high school diploma, 1–3 years of college or equivalent or 4 year college degree or graduate/professional school), income level (7 categories), body mass index, religion (Jewish and other), self-reported allergies and autoimmune diseases and pack-years of smoking. Marital status and level of education had the greatest effect on risk estimates and were included in all models. Other variables were evaluated sequentially by adding them into models containing the matching factors, marital status and education. For continuous variables, trend tests were computed among the exposed only by comparing the change in log-likelihood of models with and without the factor of interest.[26] Two-sided *p*-values are reported. Effect modification by age at tumor diagnosis (<50 and ≥50 years) and menopausal status at tumor diagnosis were explored by stratified analysis. Proxy interviews were excluded from the final models to determine whether the results changed appreciably. In addition, to determine whether the results were sensitive to the specific diagnoses included in the control group, the final regression models were refit after alternately excluding each of the major control subtypes (musculoskeletal, circulatory and digestive diseases, trauma and all other diagnoses).

## Results

Patients with glioma and meningioma tended to be slightly older (mean = 51.8 and 54.6 years respectively) than control patients (mean = 49.7 years). Both case groups had higher levels of income and were more likely to be currently married than controls (Table I). Meningioma cases were more likely to be Jewish. The vast majority of cases and controls were white, and nearly half of all study subjects were diagnosed in the Phoenix center. Associations with reproductive and hormonal variables are described separately for glioma and meningioma.

*Glioma*

Glioma cases reported a slightly later average age at menarche (13.14) than control patients (12.85). Compared to women who had begun menstruating at age 11 or younger, women whose menarche occurred at age 14 or older had an OR of 1.90 (95% CI = 1.09–3.32) of developing glioma (Table II). Women who had ever been pregnant had a somewhat lower risk of glioma than those who had not, and there was a borderline statistically significant trend of decreasing risk with increasing number of pregnancies ($p = 0.04$); however, most of the decrease occurred in women with 4 or more pregnancies. A similar pattern occurred for live births, although the trend was not statistically significant, and the reduced risk was apparent only among women with 5 or more live births. Compared to being nulliparous, having an early age at first birth was protective [OR = 0.43 (95% CI = 0.23–0.83) for a first birth <20]. Among parous women, the risk of glioma was higher for those with older ages at first birth (ORs = 1.63, 2.13, and 1.73 for 20–24, 25–29, and 30+ *vs*. <20 at first birth, respectively), but these estimates were somewhat dampened (ORs = 1.57, 1.99 and 1.54 for 20–24, 25–29, and 30+ *vs*. <20 at first birth, respectively) when the number of live births was also controlled in the model. Results for gravidity and parity differed somewhat according to menopausal status (Table III), although the test for interaction was not statistically significant ($p = 0.25$). The odds ratios for premenopausal women who had ever been pregnant or had a live birth were slightly elevated, whereas among postmenopausal women, the protective effects appeared to be stronger, but the trends for number of pregnancies ($p = 0.18$) and live births ($p = 0.17$) were not statistically significant. The results for age at menarche were slightly stronger among premenopausal women, but there was no evidence of effect modification.

Only 48% of parous glioma cases and 48% of parous controls reported that they had breast-fed 1 or more children, and few women reported breast-feeding for long periods of time. Breast-feeding was not associated with the risk of glioma among women who had borne at least 1 child (Table II). Menopausal status had little effect on the occurrence of glioma; the OR for postmenopausal women compared to premenopausal women was 0.85 (95% CI = 0.48–1.50). These results did not vary markedly according to whether menopause occurred naturally (OR = 0.92; 95% CI = 0.46–1.82) or surgically (OR = 0.72; 95% CI = 0.40–1.31). Average age at natural menopause was slightly older among glioma cases compared to controls (mean = 49.6 *vs*. 48.1 years). Women who reported natural menopause at older ages had a higher risk of glioma than women who had natural menopause at an early age; OR (95% CI) = 2.33 (0.92–5.92) for menopause at age 48-51, and 1.90 (0.71–5.06) for ages 52 and older, compared to women with a natural menopause before age 48. Having had a bilateral oophorectomy had little effect, and there were no discernible trends according to the age at which bilateral oophorectomy occurred or the number of years since bilateral oophorectomy (data not shown).

Women who reported having ever used oral contraceptives had a reduced risk of glioma, but there were no consistent patterns with respect to duration of use or age at first use (Table IV). Risk of glioma tended to decline with increasing number of years since first use of oral contraceptives ($p = 0.03$). Similarly, time since last use also showed greater reductions in risk for more years since last use. However, when the models were stratified by age at diagnosis (<50 *vs*. 50 and older), the apparent protective effects of past oral contraceptive use were seen only among women over 50 (Table V). Glioma also occurred less commonly among postmenopausal women who reported having used hormone replacement therapy, but there were no consistent trends by length of use; HRT use for less than 1 year had a lower OR than use for 10 or more years (Table IV). When duration of use of HRT was stratified according to current and recent use (<5 years) versus former use (≥5 years) of HRT, there were no consistent patterns (data not shown). There were also no remarkable patterns by age at first use

**TABLE I** – DISTRIBUTION OF BRAIN TUMOR CASES AND CONTROL PATIENTS WITH RESPECT TO SELECTED CHARACTERISTICS, U.S. HOSPITAL-BASED CASE-CONTROL STUDY, 1994–1998

| Characteristic | Number (%) | | |
|---|---|---|---|
| | Controls | Glioma[1] | Meningioma |
| | 436 (100) | 212 (100) | 151 (100) |
| Location of hospital[2] | | | |
| Phoenix | 210 (48) | 99 (47) | 77 (51) |
| Boston | 127 (29) | 67 (32) | 59 (39) |
| Pittsburgh | 99 (23) | 46 (22) | 15 (10) |
| Age at interview, years[2,3] | | | |
| 18–39 | 132 (30) | 57 (27) | 26 (17) |
| 40–59 | 173 (40) | 78 (37) | 70 (46) |
| 60–90 | 131 (30) | 77 (36) | 55 (36) |
| Race/ethnicity[2] | | | |
| White, non-Hispanic | 381 (87) | 188 (89) | 127 (84) |
| White, Hispanic | 33 (8) | 13 (6) | 11 (7) |
| Black | 13 (3) | 5 (2) | 5 (3) |
| Asian | 1 (0) | 2 (1) | 3 (2) |
| Native American | 5 (1) | 2 (1) | 1 (1) |
| Other/unknown | 3 (1) | 2 (1) | 4 (3) |
| Highest education level | | | |
| <high school | 58 (13) | 33 (13) | 15 (10) |
| High school/GED | 124 (28) | 58 (27) | 49 (32) |
| 1–3 years college | 144 (33) | 62 (29) | 52 (34) |
| 4-year college | 55 (13) | 27 (13) | 17 (11) |
| Graduate/professional | 45 (10) | 26 (12) | 17 (11) |
| Unknown | 10 (2) | 6 (3) | 1 (1) |
| Self-reported household income ($1,000s) | | | |
| <15 | 80 (18) | 27 (13) | 12 (8) |
| 15–<25 | 64 (15) | 38 (18) | 27 (18) |
| 25–<35 | 59 (14) | 31 (15) | 23 (15) |
| 35–<50 | 80 (18) | 33 (16) | 23 (15) |
| 50–<75 | 67 (15) | 30 (14) | 22 (15) |
| ≥75 | 59 (13) | 44 (21) | 29 (19) |
| unknown | 27 (6) | 9 (4) | 15 (10) |
| Marital status | | | |
| Currently married | 215 (49) | 134 (63) | 98 (65) |
| Widowed | 64 (15) | 18 (8) | 19 (13) |
| Divorced | 72 (17) | 23 (11) | 21 (14) |
| Separated | 18 (4) | 7 (3) | 3 (2) |
| Never married | 67 (15) | 30 (14) | 10 (7) |
| Religion | | | |
| Catholic | 189 (43) | 86 (41) | 71 (47) |
| Protestant | 165 (38) | 86 (41) | 43 (29) |
| Jewish | 11 (3) | 9 (4) | 15 (10) |
| Other or none | 70 (16) | 31 (15) | 21 (14) |

[1]Includes glioma and neuroepitheliomatous tumors (ICD-O-2 morphology codes 9380–9473, 9490–9506[24]). Includes 102 glioblastomas, 3 gliosarcomas, 24 anaplastic astrocytomas, 16 other or unspecified astrocytomas, 24 oligodendrogliomas, 2 anaplastic oligodendrogliomas, 15 mixed gliomas, 5 ependymomas, 2 anaplastic ependymomas, 1 subependymal gliomas, 5 gangliogliomas, 3 neurocytomas, 2 medulloblastomas, 2 neuroblastomas, and 6 gliomas of unspecified type.–[2]Matching variable.–[3]Age at interview, age at tumor diagnosis (cases) and age at hospital admission were nearly identical.

or years since first use of HRT. Women who had not used HRT for 10 or more years prior to the reference date had the lowest risk of glioma. A total of 33 (15.6%) glioma patients had proxy interviews only, *vs.* 7 (1.6%) control patients. Findings from analyses that excluded proxy interviews were generally similar to those including all study subjects, although the results for age at menarche became somewhat stronger (OR = 2.03 for age at menarche ≥14 *vs.* <12) and the findings for age at first birth somewhat weaker (OR = 0.52 for a first birth <20 *vs.* nulliparous women). Sensitivity analyses excluding major control subgroups also did not change the odds ratios markedly (data not shown).

*Meningioma*

Overall, there were few notable findings for meningioma. Age at menarche was not related to the risk of meningioma (Table II). There was a small increase in risk of meningioma for ever-gravid women but no consistent trend with the number of pregnancies. Similarly, ever-parous women had a higher risk than nulliparous women, but the risk was higher for women with 2 or 3 live births than for those with 4 or more births. Women with a first birth before age twenty had lower risk than those with later first births, but the trend was not statistically significant. Among women who had had 1 or more live births, a longer duration of lactation was associated with a lower risk, but the number of women in the longest duration category was too small to evaluate this association with precision.

Overall, menopausal status was unrelated to risk (OR = 1.13 (95% CI = 0.61–2.09) for postmenopausal women), but women who had been through a natural menopause had a somewhat higher risk of meningioma (OR = 1.52 (95% CI = 0.74–3.13)), compared to premenopausal women of similar age (Table II). Women who had a later age at menopause were more likely to be diagnosed with meningioma ($p = 0.09$), and the trend was slightly more pronounced when patients with proxy-only interviews were excluded (data not shown). The odds ratio estimates for age at menopause also increased when the analysis was restricted to women who had a natural menopause [OR = 1.56 (95% CI = 0.59–4.13) at age 48–51, and OR = 2.28 (95% CI = 0.82–6.36) for women with natural menopause at age 52 or older, compared

**TABLE II** – RISK OF GLIOMA AND MENINGIOMA WITH RESPECT TO REPRODUCTIVE VARIABLES, U.S. HOSPITAL BASED CASE-CONTROL STUDY, 1994–1998

| | Controls *N* | *N* | Glioma OR[1] (95% CI) | *N* | Meningioma OR[1] (95% CI) |
|---|---|---|---|---|---|
| Age at menarche | | | | | |
| ⩽11 | 82 | 26 | 1.00 | 27 | 1.00 |
| 12–13 | 218 | 105 | 1.69 (1.01–2.83) | 72 | 1.17 (0.68–2.01) |
| ⩾14 | 119 | 67 | 1.90 (1.09–3.32) | 41 | 0.95 (0.52–1.72) |
| Missing | 17 | 14 | | 11 | |
| | | | $p = 0.07$ | | $p = 0.52$ |
| Ever pregnant | | | | | |
| No | 75 | 36 | 1.00 | 15 | 1.00 |
| Yes | 353 | 171 | 0.89 (0.54–1.47) | 132 | 1.22 (0.63–2.37) |
| Missing | 8 | 5 | | 4 | |
| Number of pregnancies | | | | | |
| 0 | 75 | 36 | 1.00 | 15 | 1.00 |
| 1–2 | 131 | 67 | 0.97 (0.57–1.69) | 52 | 1.41 (0.70–2.85) |
| 3 | 82 | 43 | 0.94 (0.52–1.73) | 28 | 1.09 (0.50–2.37) |
| 4+ | 140 | 61 | 0.73 (0.41–1.30) | 51 | 1.07 (0.52–2.21) |
| | | | $p = 0.04$ | | $p = 0.47$ |
| Ever had live birth | | | | | |
| No | 101 | 48 | 1.00 | 22 | 1.00 |
| Yes | 327 | 159 | 0.85 (0.54–1.35) | 125 | 1.33 (0.75–2.36) |
| Missing | 8 | 5 | | 4 | |
| Number of live births | | | | | |
| 0 | 101 | 48 | 1.00 | 22 | 1.00 |
| 1 | 63 | 30 | 0.97 (0.54–1.75) | 17 | 1.08 (0.51–2.30) |
| 2 | 108 | 52 | 0.85 (0.50–1.44) | 49 | 1.59 (0.85–2.99) |
| 3 | 64 | 35 | 0.90 (0.49–1.65) | 26 | 1.48 (0.71–3.09) |
| 4 | 47 | 28 | 0.91 (0.47–1.79) | 13 | 0.72 (0.31–1.71) |
| 5+ | 45 | 14 | 0.45 (0.21–0.99) | 20 | 1.35 (0.61–2.97) |
| Missing | 8 | 5 | | 4 | |
| | | | $p = 0.18$ | | $p = 0.60$ |
| Age at first live birth | | | | | |
| Nulliparous | 101 | 48 | 1.00 | 22 | 1.00 |
| <20 | 96 | 26 | 0.43 (0.23–0.83) | 28 | 1.05 (0.53–2.20) |
| 20–24 | 135 | 70 | 0.89 (0.53–1.50) | 53 | 1.25 (0.66–2.36) |
| 25–29 | 61 | 40 | 1.24 (0.69–2.23) | 28 | 1.71 (0.85–3.47) |
| 30+ | 35 | 21 | 1.04 (0.52–2.07) | 15 | 1.34 (0.60–3.01) |
| Missing | 8 | 7 | | 5 | |
| | | | $p = 0.05$ | | $p = 0.92$ |
| Menopausal status | | | | | |
| Premenopausal | 187 | 86 | 1.00 | 47 | 1.00 |
| Postmenopausal | 244 | 124 | 0.85 (0.48–1.50) | 101 | 1.13 (0.61–2.09) |
| Missing | 5 | 2 | | 3 | |
| Type of menopause | | | | | |
| Premenopausal | 187 | 86 | 1.00 | 47 | 1.00 |
| Natural | 105 | 63 | 0.92 (0.46–1.82) | 54 | 1.52 (0.74–3.13) |
| Surgical | 130 | 52 | 0.72 (0.40–1.31) | 42 | 0.96 (0.50–1.84) |
| Other | 6 | 4 | 1.28 (0.33–4.94) | 3 | 1.37 (0.30–6.36) |
| Missing | 8 | 7 | | 5 | |
| Age at menopause[2] | | | | | |
| <40 | 76 | 33 | 1.00 | 25 | 1.00 |
| 40–44 | 46 | 14 | 0.68 (0.31–1.51) | 10 | 0.76 (0.32–1.81) |
| 45–49 | 45 | 20 | 0.92 (0.43–2.00) | 20 | 1.27 (0.60–2.70) |
| 50+ | 61 | 44 | 1.53 (0.76–3.05) | 33 | 1.76 (0.85–3.63) |
| Missing | 20 | 14 | | 13 | |
| | | | $p = 0.50$ | | $p = 0.09$ |
| Bilateral oophorectomy[3] | | | | | |
| No | 359 | 177 | 1.00 | 121 | 1.00 |
| Yes | 67 | 30 | 0.88 (0.53–1.45) | 25 | 0.88 (0.51–1.51) |
| Missing | 10 | 5 | | 5 | |
| Ever breast fed[4] | | | | | |
| No | 165 | 78 | 1.00 | 70 | 1.00 |
| Yes | 155 | 71 | 0.95 (0.63–1.45) | 53 | 0.84 (0.52–1.33) |
| Missing | 7 | 10 | | 2 | |
| Duration of breast feeding (months)[4] | | | | | |
| 0 | 165 | 78 | 1.00 | 70 | 1.00 |
| 1–6 | 63 | 22 | 0.83 (0.44–1.56) | 17 | 0.96 (0.49–1.88) |
| 7–16 | 50 | 22 | 0.82 (0.47–1.45) | 24 | 0.91 (0.50–1.66) |
| 17+ | 42 | 27 | 1.26 (0.69–2.27) | 12 | 0.62 (0.29–1.34) |
| Missing | 7 | 10 | | 2 | |
| | | | $p = 0.21$ | | $p = 0.27$ |

[1]Controlling for matching factors (age, ethnicity, hospital, distance of residence from hospital), marital status, and education.–[2]Four women (2 patients with meningioma, 1 with glioma and 1 control patient) who reported menopause at >60 years of age included in missing age at menopause category.–[3]Bilateral oophorectomy occurring within year of interview included in "no" category.–[4]Parous women only.

**TABLE III** – RISK OF GLIOMA ACCORDING TO REPRODUCTIVE FACTORS, BY MENOPAUSAL STATUS AT THE TIME OF TUMOR DIAGNOSIS (INTERVIEW), U.S. HOSPITAL-BASED CASE-CONTROL STUDY, 1994–1998

| Reproductive factor | Premenopausal | Postmenopausal |
|---|---|---|
| Age at menarche | OR (95% CI) | OR (95% CI) |
| ⩽11 | 1.00 | 1.00 |
| 12–13 | 1.53 (0.68–3.47) | 1.65 (0.83–3.31) |
| 14+ | 2.10 (0.86–5.15) | 1.68 (0.81–3.48) |
| Ever pregnant | | |
| No | 1.00 | 1.00 |
| Yes | 1.29 (0.66–2.52) | 0.53 (0.25–1.15) |
| Number of pregnancies | | |
| None | 1.00 | 1.00 |
| 1–2 | 1.37 (0.66–2.85) | 0.59 (.25–1.37) |
| 3 | 1.65 (0.70–3.87) | 0.54 (0.22–1.31) |
| 4 or more | 0.88 (0.37–2.11) | 0.48 (0.21–1.10) |
| Ever had a live birth | | |
| No | 1.00 | 1.00 |
| Yes | 1.13 (0.61–2.08) | 0.65 (0.32–1.30) |
| Number of live births | | |
| None | 1.00 | 1.00 |
| 1 | 1.14 (0.50–2.60) | 0.77 (0.32–1.87) |
| 2 | 1.09 (0.53–2.26) | 0.71 (0.32–1.58) |
| 3 or more | 1.17 (0.53–2.60) | 0.57 (0.27–1.21) |
| Age at first live birth | | |
| Nulliparous | 1.00 | 1.00 |
| <20 | 0.40 (0.15–1.08) | 0.44 (0.18–1.10) |
| 20–24 | 1.12 (0.53–2.37) | 0.66 (0.31–1.41) |
| 25–29 | 3.26 (1.32–8.05) | 0.69 (0.30–1.59) |
| 30+ | 1.26 (0.45–3.59) | 0.79 (0.30–2.10) |

to women less than age 48 at natural menopause], but only 54 meningioma cases had undergone a natural menopause. Bilateral oophorectomy was not related to risk. Overall, there was little evidence that use of hormone replacement therapy or oral contraceptives was associated with meningioma. There was a borderline trend ($p = 0.03$) towards a reduced risk of meningioma among women who began taking hormone replacement therapy at a young age, but this result was based on relatively small numbers of cases (Table IV). There was no statistically significant relationship between duration of use or time since first or last use of either exogenous hormone.

## Discussion

Our results do not provide consistent evidence of a strong link between hormonal factors and brain tumors; however, there were some intriguing findings, particularly for glioma. There was an approximately 50% lower risk of glioma among women who reported earlier menarche or early age at first birth. These results were not sensitive to exclusion of women with a proxy interview and did not vary when subgroups of control patients, such as those with trauma or circulatory diseases, were excluded. Also, these findings were similar when results were stratified by age or menopausal status, and when additional potential confounding variables were considered. Use of oral contraceptives or hormone replacement therapy also was associated with a lower risk of glioma, but there was little evidence of dose-response according to years of use, and the findings for oral contraceptives were apparent only in older women. Few associations emerged between meningioma and reproductive factors, except for a slight reduction in risk among women who began taking hormone replacement therapy at an early age and a borderline increase in risk among women with an older age at menopause.

To our knowledge, ours is the first study to examine the relationship between age at menarche and glioma risk. If the association is real, it may be related to long-term changes in levels of steroid sex hormones or associated proteins in women who have an early menarche. Madigan found significant inverse relationships between recalled age at menarche and levels of androstenedione, estrone, estradiol and bioavailable estradiol among postmenopausal women.[27]. Two other cross-sectional studies in both premenopausal[28] and postmenopausal[29] women have reported higher levels of estradiol among women with an early age at menarche, but others have been inconsistent.[27,28,30–32] Two studies have reported lower levels of sex hormone binding globulin (SHBG) in women who had an early menarche,[33,34] but others have not found differences.[27,30,32] The inconsistencies of cross-sectional studies may be due to nondifferential misclassification of recalled age at menarche or inaccurate hormone measurements, especially since these studies usually relied on only 1 measurement. In the only prospective study that has been reported, 200 girls between the ages of 7 and 17 were followed to early adulthood with questionnaires and steroid hormone measurements from 1974 through 1987.[35] Women who had menarche before age 12 had significantly higher follicular-phase levels of estradiol and significantly lower levels of SHBG compared to those with a later menarche. Similar findings were apparent during late adolescence.[36]

It is well known that steroid hormones affect the developing brain, resulting in gender differences in brain structure and function. Estrogen also is thought to have neuroprotective effects,[37] possibly through its antioxidant properties or through activation of growth-signaling pathways, and women have been shown to recover more fully than men after traumatic brain injury.[38] Estrogen reduces glutamate toxicity in glial cells[39] and speeds up the process of repair after brain trauma.[40] Significant changes in brain development occur throughout childhood and adolescence, and experimental evidence suggests that developing glial cells are more susceptible to DNA damage than fully differentiated cells.[41,42] Earlier exposure to regular menstrual cycles and the concomitant earlier increase in exposure to estrogens may protect against tumor initiation during this early life stage. Alternatively, women with an early menarche may have higher estrogen levels over the long-term, which may provide ongoing protection against damage to glial cells. It also is possible that early menarche is a marker of more rapid development, including brain development, and that more rapid brain development shortens the time window of elevated susceptibility to neurocarcinogens.

We found a statistically significant reduced risk of glioma among women who had their first full-term live birth before age 20 and a borderline trend towards increasing risk with first births at older ages, consistent with an earlier study.[18] We found only a slight reduction in risk of glioma according to either gravidity or parity. Although these results were not statistically significant, the association was in the same direction as that reported by several other brain tumor studies, including a large linked-registry study in Sweden.[17,18,20] Similar to findings for breast cancer, results were somewhat different among premenopausal and postmenopausal women. There was a slight increase in risk among gravid and/or parous premenopausal women but a more pronounced reduction in risk among postmenopausal women. The distribution of histopathologic subtypes of glioma diagnosed at older ages differs from that at younger ages, and etiologic factors may also be different.

Estrogen and progesterone levels rise dramatically during pregnancy.[43] Parallel to the findings for age at menarche, exposure to high levels of pregnancy hormones at an early age may protect against glioma initiation. On the other hand, many hormonal changes occur following a first pregnancy, including a long-term lowering of levels of prolactin, estradiol, and androgens, and long-term higher levels of estriol.[32,44–47] Prolactin has been shown to stimulate cell proliferation in cultured astrocytes and glioma cells,[48,49], and it is conceivable that higher prolactin levels in nulliparous women may promote tumor growth.

We found no indication that menopausal status or a history of bilateral oophorectomy affected the risk of glioma, in contrast to Schlehofer,[50] who reported a significantly elevated risk of glioma in postmenopausal women. Previous studies have not evaluated glioma in relation to age at menopause; we found a suggestion of an increased risk of glioma among women with later age at natural

**TABLE IV** – RISK OF GLIOMA AND MENINGIOMA ACCORDING TO USE OF EXOGENOUS HORMONES, U.S. HOSPITAL-BASED STUDY, 1994–1998

| | Controls | Glioma | OR (95% CI)[1] | Meningioma | OR (95% CI)[1] |
|---|---|---|---|---|---|
| Oral contraceptive use[2] | | | | | |
| Never | 170 | 102 | 1.00 | 61 | 1.00 |
| Ever | 258 | 100 | 0.66 (0.44–1.00) | 84 | 1.02 (0.63–1.66) |
| Missing | 8 | 10 | | 6 | |
| Duration of use | | | | | |
| Never | 170 | 102 | 1.00 | 61 | 1.00 |
| <1 year | 47 | 19 | 0.69 (0.37–1.31) | 9 | 0.58 (0.25–1.36) |
| 1–4 | 96 | 39 | 0.68 (0.41–1.12) | 24 | 0.81 (0.43–1.52) |
| 5–9 | 60 | 15 | 0.40 (0.20–0.79) | 27 | 1.51 (0.79–2.90) |
| 10+ | 47 | 22 | 0.85 (0.45–1.59) | 14 | 0.82 (0.39–1.74) |
| | | | $p = 0.57$ | | $p = 0.92$ |
| Missing | 16 | 15 | | 16 | |
| Age at first use | | | | | |
| Never | 170 | 102 | 1.00 | 61 | 1.00 |
| <18 | 50 | 14 | 0.43 (0.20–0.90) | 5 | 0.42 (0.14–1.24) |
| 18–20 | 78 | 32 | 0.72 (0.40–1.27) | 21 | 0.80 (0.40–1.58) |
| 21–24 | 65 | 28 | 0.81 (0.45–1.44) | 22 | 1.10 (0.56–2.17) |
| 25+ | 58 | 20 | 0.54 (0.29–0.99) | 25 | 0.92 (0.49–1.72) |
| | | | $p = 0.03$ | | $p = 0.16$ |
| Missing | 15 | 16 | | 17 | |
| Years since first use | | | | | |
| Never | 170 | 102 | 1.00 | 61 | 1.00 |
| ≤10 | 47 | 26 | 1.37 (0.62–3.02) | 4 | 0.73 (0.19–2.76) |
| 11–20 | 65 | 26 | 0.90 (0.44–1.82) | 22 | 1.33 (0.62–2.86) |
| 21–30 | 100 | 33 | 0.52 (0.30–0.91) | 33 | 0.75 (0.41–1.38) |
| 31+ | 39 | 9 | 0.37 (0.16–0.83) | 14 | 0.84 (0.39–1.81) |
| Missing | 15 | 16 | | | |
| | | | $p = 0.03$ | | $p = 0.59$ |
| Years since last use | | | | | |
| Never | 170 | 102 | 1.00 | 61 | 1.00 |
| Current | 27 | 18 | 1.57 (0.70–3.56) | 6 | 1.33 (0.43–4.12) |
| 1–9 yr | 50 | 25 | 1.09 (0.52–2.29) | 10 | 1.18 (0.45–3.05) |
| 10–19 | 69 | 19 | 0.48 (0.25–0.92) | 24 | 1.01 (0.52–1.95) |
| 20+ | 102 | 32 | 0.51 (0.30–0.85) | 33 | 0.78 (0.43–1.39) |
| | | | $p = 0.12$ | | $p = 0.27$ |
| Missing | 18 | 16 | | 17 | |
| Hormone replacement therapy (HRT)[2,3] | | | | | |
| Never | 110 | 62 | 1.00 | 49 | 1.00 |
| Ever | 124 | 51 | 0.66 (0.41–1.09) | 50 | 0.84 (0.50–1.39) |
| Missing | 10 | 11 | | 2 | |
| Duration of use of HRT | | | | | |
| Never | 110 | 62 | 1.00 | 49 | 1.00 |
| <1 year | 23 | 8 | 0.61 (0.24–1.54) | 9 | 0.99 (0.40–2.42) |
| 1–4 | 34 | 12 | 0.62 (0.29–1.34) | 14 | 0.96 (0.45–2.06) |
| 5–9 | 23 | 9 | 0.55 (0.22–1.34) | 9 | 0.80 (0.32–1.99) |
| 10+ | 38 | 20 | 0.86 (0.43–1.72) | 17 | 0.82 (0.40–1.72) |
| | | | $p = 0.30$ | | $p = 0.99$ |
| | 16 | 13 | | 3 | |
| Age started HRT | | | | | |
| Never used | 110 | 62 | 1.00 | 49 | 1.00 |
| <40 | 35 | 12 | 0.66 (0.30–1.46) | 9 | 0.50 (0.21–1.20) |
| 40–44 | 26 | 7 | 0.47 (0.18–1.21) | 8 | 0.80 (0.32–2.01) |
| 45–49 | 25 | 13 | 0.79 (0.35–1.77) | 13 | 1.00 (0.45–2.24) |
| 50+ | 33 | 14 | 0.60 (0.28–1.26) | 19 | 1.17 (0.58–2.38) |
| | | | $p = 0.65$ | | $p = 0.03$ |
| Missing | 15 | 16 | | 3 | |
| Years since first use of HRT | | | | | |
| Never used | 110 | 62 | 1.00 | 49 | 1.00 |
| <5 | 30 | 12 | 0.70 (0.32–1.57) | 20 | 1.90 (0.90–4.02) |
| 5–10 | 26 | 5 | 0.24 (0.08–0.71) | 7 | 0.50 (0.19–1.30) |
| 11–20 | 22 | 10 | 0.79 (0.34–1.85) | 8 | 0.69 (0.27–1.75) |
| 21+ | 41 | 19 | 0.75 (0.37–1.51) | 14 | 0.66 (0.31–1.42) |
| | | | $p = 0.27$ | | $p = 0.09$ |
| Missing | 15 | 16 | | 3 | |
| Years since last used HRT | | | | | |
| Never used | 110 | 62 | 1.00 | 49 | 1.00 |
| Current use | 76 | 33 | 0.72 (0.41–1.26) | 32 | 0.88 (0.49–1.58) |
| 1–9 | 10 | 3 | 0.57 (0.13–2.47) | 9 | 2.22 (0.79–6.19) |
| 10+ | 31 | 10 | 0.48 (0.21–1.11) | 7 | 0.48 (0.19–1.23) |
| | | | $p = 0.25$ | | $p = 0.22$ |
| Missing | 17 | 16 | | 4 | |

[1]Controlling for matching factors, marital status and education.–[2]Use solely within one year of reference date counted as nonuse.–[3]HRT question asked of postmenopausal women only.

**TABLE V** – RISK OF GLIOMA ACCORDING TO ORAL CONTRACEPTIVE USE, STRATIFIED BY AGE AT DIAGNOSIS OR INTERVIEW, U.S. HOSPITAL-BASED CASE-CONTROL STUDY, 1994–1998

| Oral contraceptive use | <50 N = 98/228 | ≥50 N = 114/208 |
|---|---|---|
| | OR (95% CI) | OR (95% CI) |
| Never | 1.00 | 1.00 |
| Ever | 1.25 (0.67–2.34) | 0.37 (0.20–0.69) |
| Duration of use | | |
| None | 1.00 | 1.00 |
| <1 yr | 1.34 (0.56–3.21) | 0.46 (0.16–1.29) |
| 1–4 years | 1.21 (0.59–2.50) | 0.43 (0.18–1.01) |
| 5–9 years | 0.83 (0.36–1.93) | 0.08 (0.01–0.66) |
| 10+ | 1.70 (0.73–3.94) | 0.37 (0.11–1.22) |
| Age at 1st use | | |
| No use | 1.00 | 1.00 |
| <18 | 0.74 (0.32–1.74) | [1] |
| 18–20 | 1.42 (0.69–2.92) | [1] |
| 21–24 | 1.51 (0.69–3.30) | 0.63 (0.23–1.81) |
| 25+ | 1.00 (0.32–31.3) | 0.51 (0.25–1.07) |
| Years since 1st use | | |
| No use | 1.00 | 1.00 |
| ≤10 | 1.57 (0.68–3.63) | [1] |
| 11–19 | 1.12 (0.50–2.51) | 2.94 (0.22–38.8) |
| 21–30 | 0.99 (0.44–2.25) | 0.26 (0.11–0.63) |
| 31+ | [1] | 0.33 (0.14–0.78) |
| Years since last use | | |
| No use | 1.00 | 1.00 |
| Current | 1.84 (0.17–4.43) | [1] |
| 1–9 | 1.26 (0.55–2.87) | 1.31 (0.07–24.1) |
| 10–19 | 0.77 (0.34–1.72) | 0.25 (0.06–0.99) |
| 20+ | 1.10 (0.46–2.63) | 0.33 (0.16–0.68) |

[1]No observations.

menopause, but the trend was not statistically significant and the number of cases was small. An hypothesis that prolonged exposure to high levels of estrogen is protective against glioma would predict increased risk associated with *earlier* age at natural menopause.

Similar to findings from a multi-center, international brain tumor study,[50] we found a lower risk of glioma among users of both oral contraceptives and postmenopausal hormone replacement therapy. However, there was no dose-response relationship for either type of hormone preparation according to duration of use. For oral contraceptives, there were borderline trends of reduction in the risk of glioma according to the age and year of first use of oral contraceptives. When the data on oral contraceptives were stratified by age at diagnosis, reduced risks were seen only among older women, who are more likely to have been exposed to more potent OCs. It is possible that the higher potency formulations of OCs used in the 1960s and 1970s had protective effects, while OCs containing lower levels of estrogen and progesterone, which have predominated since the mid-1970s, have little or no effect on glioma risk.

The most suggestive evidence for a role of hormonal exposures in meningioma occurrence is the higher risk among women, which is most pronounced during the reproductive years. However, many meningiomas are slow-growing and first diagnosed at autopsy,[51] and it is possible that the female excess may be, at least in part, a diagnostic artifact related to greater use of medical care among women in the U.S.[52] A Mayo Clinic study[53] found a slightly higher incidence of meningioma among males diagnosed at autopsy, although there was still a female excess overall when both clinical and autopsy cases were included in the incidence rates. Possibly, female hormones promote growth of meningioma, leading to earlier symptoms and diagnosis in women.

As noted previously, there were few associations between meningioma and reproductive factors in our study. In contrast to a recent report from the Nurses Health Study,[54] there was no association between age at menarche and meningioma. Ever-gravid and ever-parous women had slightly higher risks of meningioma, in contrast to the slightly lower risks for glioma, but these results were not significant, and there were no trends according to number of births or age at first birth. We found a small, nonsignificant increase in risk among women who had undergone a natural menopause compared to premenopausal women of the same age but no increase among women who reported a surgically induced menopause. Previous studies have reported both decreased[23,54] and slightly increased risks[50] among women with natural menopause. We found a suggestion of an increase in meningioma risk with increasing age at menopause, which was stronger among women with a natural menopause. Parallel to the association between breast cancer and age at menopause, these findings might imply that longer exposure to estrogen increases the risk of meningioma. However, in contrast to previous findings for breast cancer, we found no association between use of postmenopausal hormones and meningioma, so the results do not provide a coherent picture.

Strengths of our study include a high participation rate among both cases and controls, interviews conducted soon after diagnosis, a low proportion of proxy interviews, and collection of data on numerous reproductive factors and potential confounding variables.

Our study also has several important limitations. First, the number of cases was small, and we may have lacked statistical power, particularly for meningioma. Second, misclassification of exposure history is always of concern in a study such as this. Cases may recall suspected exposures more accurately than controls, leading to spurious elevations in risk.[55] On the other hand, in our study, cases may have had more difficulty remembering exposure history than controls because of cognitive impairments that often accompany glioma progression. Differential lack of recall may have resulted in lower risk estimates for oral contraceptives and hormone replacement therapy, if glioma cases had more difficulty recalling past exposures to these drugs than control patients. Deficient recall by glioma cases might have been greater among those diagnosed at older ages, as the proportion of glioblastoma and other high-grade tumors increases with age, and such tumors are more likely to cause mental status impairments.[56] However, for other variables, such as age at menarche, nondifferential misclassification, and bias towards the null, seem more likely. In general, reproductive history is well-recalled by women. Bean[57] found that 75% to 90% of women were able to recall age at menarche, age at natural or surgical menopause and age at first use of oral contraceptives to within 1 year. Bosetti[58] also found good reliability for reproductive history variables (kappa >0.80) among 294 hospital controls who were reinterviewed 1 to 4 years after an initial interview, and Must[59] reported a high correlation between actual and recalled age at menarche. Studies of recall of oral contraceptive use have found good agreement between interview and pharmacy records.[60] Our study also is limited by the lack of details collected on types of oral contraceptives and hormone replacement therapy. For example, we had no ability to evaluate whether there were different effects for estrogen alone *vs*. combined estrogen and progestin hormone replacement therapy. We did not collect information on use of hormone replacement therapy among premenopausal women. We also lacked details on age at last birth, and we did not collect data on breast feeding history for individual children, only the average length of time overall.

Despite the limitations, our study is one of the most comprehensive to date to evaluate whether reproductive and hormonal factors are associated with the risk of malignant and benign brain tumors. Overall, we found some associations between glioma and reproductive history that point to the possible role of reproductive hormone exposure early in life on glioma risk. Both early age at menarche and early age at first birth were associated with an approximate 50% reduction in glioma risk. Although we did not find significant effects for parity, our results are consistent with several previous studies that reported a reduction in risk of glioma among parous women. Also, we observed reduced risks of glioma for use of both oral contraceptives and hormone replacement therapy, in agreement with a prior study.[50]

However, the lack of association between duration of use and risk suggests that this finding may be due to chance or differential recall. Despite potentially more suggestive biological evidence for an association between meningioma and hormonal exposures, we found little indication in our study that reproductive factors affect risk of meningioma.

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